PATENT ABSTRACTS OF JAPAN

(11)Publication number : **09-291031**

(43)Date of publication of application : **11.11.1997**

(51)Int.Cl. **A61K 31/41**

A61K 31/41

A61K 31/41

C07D271/06

// C07M 7:00

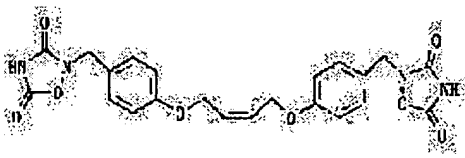
(21)Application number : **08-102878**

(22)Date of filing : **24.04.1996**

(71)Applicant : **YAMANOUCHI PHARMACEUT CO LTD**

(72)Inventor : **SHIBAZAKI MASAYUKI**
HIRAYAMA REIKO
SHIMATANI AKIYOSHI
NIIGATA KUNIHIRO

(54) **LIPID METABOLISM IMPROVER**



(57)Abstract:
PROBLEM TO BE SOLVED: To obtain a lipid metabolism improver comprising a specific compound as an active ingredient effective for preventing and treating diseases to be estimated cause deterioration of symptoms resulting from hyperlipemia, etc., having improving action in lipid metabolism abnormality.
SOLUTION: This lipid metabolism improver comprises 1,4-bis[4-[(3,5- dioxo-1,2,4-oxidiazolidin-2-yl)methyl]-2-butene or its pharmacologically permissible salt as an active ingredient. A cis(Z) isomer of the formula ids preferably as the compound. A dose is generally 1-1,000mg per adult daily by oral administration and 0.1-100mg by parental administration.

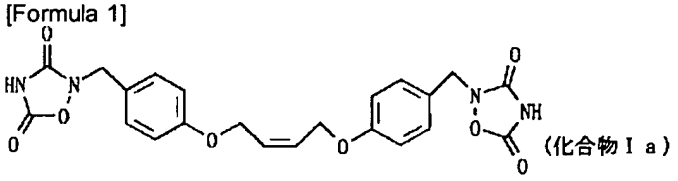
CLAIMS

[Claim(s)]
[Claim 1] The lipid-metabolism improvement agent which makes an active principle a 1 and 4-screw [- [(3, 5-dioxo - 1, 2, and 4-****** diazo lysine-2-****)methyl] phenoxy]-2-butene or its salt permitted pharmaceutically. [4]
[Claim 2] (Z) Lipid-metabolism improvement agent according to claim 1 which makes an active principle a -1 and 4-screw [- [(3, 5-dioxo - 1, 2, and 4-****** diazo lysine-2-****)methyl] phenoxy]-2-butene or its salt permitted pharmaceutically. [4]
[Claim 3] The lipid-metabolism improvement agent according to claim 1 which is prevention / treatment agent of low HDL ****.
[Claim 4] The lipid-metabolism improvement agent according to claim 1 which is prevention / treatment agent of the hyperlipidemia which joins from diabetes.

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[The technical field to which invention belongs] this invention relates to the lipid-metabolism improvement agent which makes an active principle a 1 and 4-screw [- [(3, 5-dioxo - 1, 2, and 4-****** diazo lysine-2-****)methyl] phenoxy]-2-butene or its salt permitted pharmaceutically. [4]
[0002]
[Description of the Prior Art] The arteriosclerosis nature morbus is the morbus positioned in the high precedence of the cause of death, a upward tendency is presented with change of eating habits, and the research of its prevention and treatment is advanced. Hyperlipidemia is known as the first risk factor of the arteriosclerosis nature morbus or a lock out nature heart disease. According to the second report (ATP II) of the U.S. cholesterol educational program technical committee in 1993 As positive risk factor of the coronary-arteries morbus, ** quantity LDL cholesterol, ** Age (those who are the female who greeted the menopause at 45 or more years old of males, 55 or more years old of female, and the early stage, and have not received the estrogen replacement therapy), ** Family-history [of the coronary-arteries morbus], ** smoking, ** hypertension, ** low HDL cholesterol (below 35mg / dl), and ** diabetes ** is mentioned, and high HDL cholesterol (>=60mg/dl) is shown as negative risk factor. That is, the high LDL cholesterol and low HDL cholesterol (below 35mg / dl) which are the abnormalities of a lipid metabolism become the big factor of the coronary-arteries morbus, and it is reported on the contrary that high HDL cholesterol (>=60mg/dl) works to a prevention of the coronary-arteries morbus.
[0003] Therefore, it is expected that normalization of the lipid metabolism containing an improvement of the lipid metabolism in hyperlipidemia, i.e., a fall of LDL value and elevation of HDL value, reduces the risk of the arteriosclerosis nature morbus. Especially, in a diabetic, the arteriosclerosis nature morbus of a core and a brain serves as the direct cause of death in many cases, and the importance of the prevention and treatment of the hyperlipidemia which joins from diabetes is pointed out as diabetes is further mentioned as positive risk factor of the aforementioned coronary-arteries morbus (a diagnosis, treatment Vol.80(9), 1692-1696 (1992)).
[0004] Although the first phase of the treatment of the hyperlipidemia which joins from diabetes is the alimentary therapy, in many cases, the pharmacotherapy is needed further and various hyperlipidemia therapeutic drugs are used. However, in a commercial hyperlipidemia therapeutic drug, cautions are needed in many cases in respect of the safety of a side effect or the combined use with other agents (a diagnosis, treatment Vol.80(9), 1692-1696 (1992)). The pioglitazone (pioglitazone) or ********** (troglitazone) which is the thiazolidinedione compound with which the development is furthered as a blood-sugar fall agent which has an insulin sensitivity potentiation having the triglyceride fall operation in blood is known (Arzneim.-forsch./Drug Res. – 40 (I) –) There is no report about the influence affect lipid metabolisms, such as LDL of Nr.2 (1990) and Diabetes, Vol.37, and 1549-58 thing (1988), and HDL. That is, the medicine it has the medicine and an improvement operation of

sufficient abnormalities in a lipid metabolism in addition to a blood-sugar fall operation is not yet known.
[0005] on the other hand – international – public presentation – WO – 94 – /– 25448 – No. – an official report – **** – the above – thiazolidinedione – a compound – completely – structure – differing – one – four – - – a screw – [– four – - – [(3, 5-dioxo - 1, 2, and 4-****** diazo lysine-2-****) – a methyl –] – a phenoxy –] – - – two – - – a butene – containing – being new – a screw However, about the lipid-metabolism improvement operation of these compounds, neither indication nor suggestion is carried out at all.
[0006]
[Problem(s) to be Solved by the Invention] The invention of the medicine with few side effects which improves the abnormalities (for example, hyperlipidemia) in a lipid metabolism which are the risk factor of the arteriosclerosis nature morbus is desired. It is anxious for the invention of a medicine having a fall operation of a hyperglycemia value and an improvement operation of the abnormalities in a lipid metabolism especially useful to the hyperlipidemia which joins from diabetes.
[0007]
[Means for Solving the Problem] The place where this invention person etc. examined medicinal action about a series of screw ****** diazo lysine derivative given in the above-mentioned international public presentation WO official report of No. 94/25448, A 1 and 4-screw [- [(3, 5-dioxo - 1, 2, and 4-****** diazo lysine-2-****)methyl] phenoxy]-2-butene (compound I) or its salt permitted pharmaceutically found out having a also unexpectedly good lipid-metabolism improvement operation, and completed this invention. [4] Especially as a lipid-metabolism improvement operation of compound I, the improvement operation of HDL value is remarkable.
[0008] That is, this invention is a lipid-metabolism improvement agent which makes an active principle a 1 and 4-screw [- [(3, 5-dioxo - 1, 2, and 4-****** diazo lysine-2-****)methyl] phenoxy]-2-butene (compound I) or its salt permitted pharmaceutically. [4] Moreover, this invention relates to low HDL **** prevention / treatment agent which makes an active principle compound I or its salt permitted pharmaceutically. Furthermore, this invention relates to prevention / treatment agent of the hyperlipidemia which joins from diabetes which makes an active principle compound I or its salt permitted pharmaceutically from compound I having a powerful blood-sugar fall operation.
[0009]
[Embodiments of the Invention] It is as follows when this invention is explained further. (Active principle) The active principle of this invention physic is a 1 and 4-screw [- [(3, 5-dioxo - 1, 2, and 4-****** diazo lysine-2-****)methyl] phenoxy]-2-butene (compound I) or its salt permitted pharmaceutically, and is a well-known compound currently indicated by the international public presentation WO official report of No. 94/25448 with the manufacturing method. [4]
[0010] The **** (Z) field and the transformer (E) field based on presence of a double bond exist, and such things or mixture which were separated can be used for compound I as an active principle of this invention physic. It is the **** (Z) field (compound Ia) preferably shown by the following formula.
[0011]
[Formula 1]



(化合物Ｉａ)

[0012] As a salt of compound I permitted pharmaceutically, since it has an acid proton to a ****** diazo lysine ring, it is a salt with a base and, specifically, the salt with organic bases, such as the salt with inorganic bases, such as trivalent metals, such as alkaline earth metal, such as alkali metal, such as sodium and a potassium, magnesium, and calcium, and aluminum, a monomethylamine, an ethylamine, a dimethylamine, a diethylamine, a trimethylamine, a triethylamine, a monoethanolamine, a diethanolamine, a triethanolamine, a cyclohexylamine, a lysine, Compound I which is the active principle of this invention physic, or its salt permitted pharmaceutically may be isolated as a hydrate, various solvates, or matter of a crystal polymorphism, and all of these isolated things and mixture are included by this

invention.
[0013] Actually, two or more crystal polymorphisms are checked by the **** (Z) field of compound I, and crystal B whose melting point besides crystal A whose melting point indicated by the example 10 of the above-mentioned international public presentation WO official report of No. 94/25448 is 139-144 degrees C is 166-7 degrees C, and crystal C which is 147-8 degrees C are also included by compound I of this invention. Especially, it is stable and crystal B which does not have hygroscopicity is desirable. Compound I of this invention can come to hand easily based on the technique which is well-known and was indicated by the aforementioned official report with the aforementioned official report. Moreover, the salt of compound I permitted pharmaceutically can be manufactured by the conventional method. When the hydrate, the solvate, or crystal polymorphism of compound I exists, these can be isolated to this contractor using the well-known separation / refining technique.
[0014] (Physic intended use) The lipid-metabolism improvement agent of this invention is a medicine which improves the abnormalities of the lipid metabolism produced for a certain ground. As a lipid metabolism being unusual, the increase in the abnormalities of the blood serum ******** roll value diagnosed as hyperlipidemia and/or blood serum triglyceride is mentioned, for example. The abnormalities with which independence, such as an increase in the very low density lipoprotein (VLDL-cholesterol) which accepts as blood serum cholesterol being unusual here as the increase in the total cholesterol and the balance of blood serum lipoprotein being unusual, and low extraordinary lipoprotein (LDL-cholesterol), a decrement of high density lipoprotein (HDL cholesterol) (especially HDL2-cholesterol), and an increase in remnant lipoprotein, or the plurality was combined are mentioned (clinical, research 72 volume 8 No., 1873 - 1879 pages). the operation whose medicine of this invention improves these abnormalities in a lipid metabolism – it has a metabolism improvement operation of HDL cholesterol especially
[0015] Furthermore, in the diabetic, the abnormalities in a lipid metabolism join to the 1/3, presenting low HDL **** is known 10% (a diagnosis, treatment Vol.80(9), 1692-1696 (1992)), and since the medicine of this invention has a blood-sugar fall operation, it is useful for a prevention and treatment of the hyperlipidemia which joined from these diabetes. Therefore, it is prevention / treatment agent of the hyperlipidemia which joins from diabetes preferably as a lipid-metabolism improvement agent of this invention.
[0016] As concrete indication of this invention medicine, it is the morbus which presents the abnormalities of a lipid metabolism, for example, hyperlipidemia (for example, high triglyceride ****, hypercholesterolemia, low HDL ****, etc.), an obesity, etc. are mentioned. It is especially useful as a prevention / treatment agent of low HDL ****. Furthermore, as morbus with which originate unusually [a lipid metabolism] and aggravation of a symptom is expected to be, the kidney morbus including brain arteriosclerosis, such as ischemic heart disease, such as arteriosclerosis, a myocardial infarction, and the stenocardia, and a cerebral infarction, or an aneurysm, and a nephrotic syndrome etc. is mentioned, and it can be used also as a prevention / treatment agent of these morbus.
[0017] (A tablet-ized method, a medication method, dose) The physic of this invention blends compound I or its salt permitted pharmaceutically, and the support for medicine manufacture permitted pharmaceutically, and is prepared as physic constituents, such as taking orally, a parenteral solid-state, and a liquid.
[0018] As a solid-state constituent for the internal use by this invention, a tablet, the pilule, a capsule, a fine-grain agent, a granule, etc. are mentioned. In such a solid-state constituent, one or the active substance beyond it is mixed with at least one inactive diluent, for example, a lactose, a mannitol, grape sugar, hydroxypropylcellulose, a crystalline cellulose, various starch, a polyvinyl pyrrolidone, magnesium aluminometasilicate, etc. The constituent may contain the lysis or solubilizing agent like additives other than an inactive diluent, for example, a lubricant like a magnesium stearate, disintegrator like a calcium carboxymethyl cellulose, a stabilizing agent like a lactose, glutamic acid, or an aspartic acid according to a conventional method. Moreover, the film of glycocalyx, such as a cane sugar, gelatin, hydroxypropylcellulose, and a hydroxypropyl-methylcellulose free-wheel-plate rate, stomach solubility, or the enteric nature matter may cover the granulatio of a tablet, the pilule, a granule, and the capsule containing granulatio by the need. Moreover, in order to raise the solubility of a tablet, well-known solubilization processing can be performed and tablet-ization can also be performed.
[0019] The inactive diluent generally used as a component of a constituent in the opacifier permitted pharmaceutically, a solution agent, the suspension, the syrup, the elixir, etc. as a

liquid constituent for internal use including the tablet gestalt, for example, a purified water, ethanol, etc. are included. This constituent may contain adjuvants, such as a wetting agent and a suspending agent, a sweetening agent, a flavor agent, an aromatic, and antiseptics in addition to an inactive diluent.
[0020] As injection for a parenteral administration, a water or non-water sterile solution agent, the suspension, and an opacifier are included. For example, distilled water for injection and a physiological saline are contained in a water solution agent and the water suspension. A propylene glycol, a polyethylene glycol, vegetable oil like olive oil, the alcohols like ethanol permitted pharmaceutically, and a surfactant like polyoxyethylene sorbitan fatty acid ester are contained in the solution agent of a non-aquosity, and the suspension. Such an aquosity and the constituent of a non-aquosity may contain adjuvants (for example, glutamic acid, an aspartic acid, etc.) and antiseptics, such as a wetting agent, a suspending agent, an emulsifier, a dispersant, a stabilizing agent (for example, lactose), lysis, or a solubilizing agent, in addition to these additives. These are sterility-ized by the combination or irradiation of filtration and a germicide which lets for example, a bacterium hold VCF pass. These can be again manufactured as a sterile solid-state constituent, and can also be made into the gestalt used by melting in sterile water or the sterile solvent for injection before use.
[0021] for using this invention for the purpose of [of the above-mentioned morbus] a prevention / treatment – usually – taking orally – or it is parenteral and a medicine is prescribed for the patient Although it changes with a patient's age, weight, a symptom, a curative effect, medication roots, etc. and it is suitably set up in consideration of these, usually, 0.1-100mg of dose is [in per adult day and internal use] preferably desirable 1-1000mg at 10-300mg and a parenteral administration, day, it is 1 time per or this is prescribed for the patient in 2 - several steps. Since the dose is changed according to the various conditions of the prevention purpose or others, an amount fewer than the above-mentioned dose domain may be enough as it.
[0022]
[Example] And this invention is explained to it still in detail. [below] [an example] In addition, of course, it is not that by which this invention should be limited to technique given in an example. The manufacture technique of the new crystal form of a (Z)-1 and 4-screw [- [(3, 5-dioxo - 1, 2, and 4-****** diazo lysine-2-****)methyl] phenoxy]-2-butene (compound Ia) which can be used as an active principle of this invention is shown in the example of a manufacture. [4]
[0023] (Example of manufacture 1)
(Z) -1, 4-screw [4-[3 and 5-dioxo - 1 and 2 – Manufacture (Z)-1 of 4-****** diazo lysine-2-**** methyl] phenoxy]-2-butene (compound Ia) crystal B, and 4-screw [- [(3, 5-dioxo - 1, 2, and 4-****** diazo lysine-2-****)methyl] phenoxy]-2-butene 4.68g [4] It suspended in 100ml of water, and after having added 9.0g of a lithium hydroxide and 1 hydrates and making it melt, 110ml of 1N hydrochloric acids was added, and it adjusted to the bottom of stirring pH 1-2. Crystal B which ****s the crystal crystallized after continuing stirring for 2 hours, dries after washing in cold water by 100ml of water, and is made into the purpose 4.5g was obtained. Melting point 166-167 degrees C [0024] (Example of manufacture 2)
(Z) -1, 4-screw [4-[3 and 5-dioxo - 1 and 2 – Manufacture (Z)-1 of 4-****** diazo lysine-2-**** methyl] phenoxy]-2-butene (compound Ia) crystal C, Acetone 20ml was added and heated to 4-screw [- [(3, 5-dioxo - 1, 2, and 4-****** diazo lysine-2-****)methyl] phenoxy]-2-butene-1 .80g, and it was made to melt in it. [4] It cooled radiationally, adding and stirring 20ml of water in a solution. Crystal C which dries after ****ing the separated crystal, and is made into the purpose 1.64g was obtained.
Melting point 147-148 degrees C [0025] The medicinal action of the active principle of this invention is checked by the following examinations.
(Example 1 of an examination) Zucker fatty which is a hereditary insulin resistance model animal The rat (it has the rat:quantity insulinemia which has a natural sideration obesity, high triglyceride ****, and a slight hyperglycemia) (a male, 9 week-old) was collected blood from the bottom tail vena of gluttony before medication start, and triglyceride, the total cholesterol, the blood sugar level, and the insulin value were measured. (Z)-1 which carried out the group division so that difference might not have such measured value in between groups, and was obtained in example 1 of manufacture, and 4-screw [- [(3, 5-dioxo - 1, 2, and 4-****** diazo lysine-2-****)methyl] phenoxy]-2-butene crystal B(following compound 1) 100mg/kg, and 300mg/kg [4] Or ********** (following CS-045) Internal use was continuously carried out compulsorily for 1 14 days once per day, having used kg as methyl-cellulose suspension

0.5% in 100 mg/kg and 300mg /. It collected blood similarly [on 8 or the 15 / medication 5 and /th], and triglyceride (TG) was measured. Furthermore, it dissected and collected blood and each cholesterol fraction (the total cholesterol (TC), HDL cholesterol (HDL), - cholesterol fractions other than HDL (non-HDL)) was measured on the 15th. In addition, the rate of change (average:%) which considered the medicine unsettled group as control and set control to 100 was computed.

[0026] (A result and consideration) Concentration change of the plasma triglyceride after **** during 14 days is shown in Table 1, and the plasma cholesterol concentration change after 14 day **** is shown in Table 2. The compound 1 showed the significant fall of TG from the 5 day of medication by ****, and the operation was stronger than CS-045. Even if it ****ed the compound 1 for 14 days, it did not give change to TC. Since HDL carried out the slight increase and non-HDL fell, this is considered because change was not seemingly given to TC. On the other hand, although CS-045 did not give change to HDL, since non-HDL showed the fall, they are considered that TC also showed the fall inclination. From these results, while the compound 1 had powerful TG fall operation as compared with well-known blood-sugar low purgative CS-045 by which TG fall operation is known, having the operation to which non-HDL is reduced and which makes HDL increase on the other hand, and having a good lipid-metabolism improvement operation was shown.

[0027]

Table 1 Concentration change of plasma triglyceride after 14 day ****

_____ test drug The number of examples TG (mg/dl) (Rate-of-change:%) _____ control 6 766.64**128.83 (100) Compound 1 100mg/kg 5 285.68** 55.27 (37)

Compound 1 300mg/kg 6 150.28 ** 16.32 * (20) CS-045 100mg/kg 6 528.22** 76.71 (69) CS-045 300mg/kg 6 396.86 ** 48.14 (52) _____ *:p<0.01 vs Control [0028]

Table 2 Plasma cholesterol concentration change after 14 day ****

_____ test drug TC (mg/dl) HDL (mg/dl) non-HDL (mg/dl) (Rate-of-change:%) (Rate-of-change:%) (rate-of-change:%)

_____ control 101.10**5.58 67.37**5.37 33.73**4.66 (100) (100) (100) 1300mg [/kg] compound 102.05**6.43 85.02**5.45 17.03**1.43 (101) (126) (50) CS-045 300mg/kg 83.80**5.94 69.92**5.02 13.88**1.43 (83) (104) _(41)_____ [0029] (Example 2 of an examination) It is Zucker fatty like the example 1 of an examination. The rat (a male, 9 week-old) was collected blood from the bottom tail vena of gluttony before medication start, and triglyceride, the total cholesterol, the blood sugar level, and the insulin value were measured. The group division was carried out so that a difference might not have such measured value in a between groups, and it carried out internal use compulsorily continuously for 1 30 days once per day as a test drug, having used compound 1 300mg/kg as methyl-cellulose suspension 0.5%. It collected blood after (the medication 1 and 2 and four weeks) similarly, and each parameter of triglyceride (TG), the blood sugar level (BG), and an insulin (IRI) was measured. Furthermore, it dissected and collected blood and each cholesterol fraction was measured on the 31st.

[0030] (A result and consideration) The plasma cholesterol concentration change Table 3 and after 30 day **** is shown for concentration change of each parameter after a four week continuous administration in Table 4. **** of a compound 1 shows a significant fall of TG after one week of medication as compared with a control group, and the improvement of high triglyceride **** was seen. The significant increase in HDL and the decrement of non-HDL were shown, without giving change to TC like the example 1 of an examination. Furthermore, in the exam, by the compound 1 medication group, as compared with the control group, the fall of an insulin (IRI) was shown from the one week back of medication, and the improvement of the high insulinemia accepted, and the fall of the blood sugar level (BG) was seen. These results are Zucker fatty which is a hereditary insulin resistance model animal. Having the operation which improves the abnormalities in a lipid metabolism at the same time a compound 1 reinforces the sensitivity of an insulin, it improves the high insulinemia in a rat and it reduces the blood sugar level is shown, and a compound 1 sets unusually [the lipid metabolism which joined from insulin non-dependency diabetes], and suggests possibility of becoming the useful medicine which improves the abnormalities of a lipid metabolism.

[0031]

Table 3 Each parameter concentration change after four week ****
_____ test drug TG (mg/dl) BG (mg/dl) IRI (ng/dl) (Rate-of-change:%) (rate-of-change:%) (rate-of-change:%) _____
control 846.3**170.3 189.3**45.1 133.6**25.8 (100) (100) (100) Compound 1 300mg/kg 183.2** 15.1 95.7**4.2 65.9**6.6 (22) * (51) (49) _____ Each six groups *:p<0.01vs Control [0032]
Table 3 Plasma cholesterol concentration change after 30 day ****
_____ test drug TC (mg/dl) HDL (mg/dl) non-HDL (mg/dl) (Rate-of-change:%) (rate-of-change:%) (rate-of-change:%)
_____ control 121.0**13.6 69.8**5.2 51.2**11.4 (100) (100) (100) Compound 1 300mg/kg 127.3**7.7 106.8**6.5 20.5**2.0 (105) (153) * (40)
_____ Each six groups *:p<0.01 vs control [0033] (Example 3 of an examination) The normal rat (SD rat) was collected blood from the bottom tail vena of gluttony before medication start, and triglyceride, the total cholesterol, the blood sugar level, and the insulin value were measured. The group division was carried out so that a difference might not have such measured value in a between groups, and it carried out internal use compulsorily continuously for 1 14 days once per day as a test drug, having used compound 1 300mg/kg as methyl-cellulose suspension 0.5%. It collected blood the medication 4 and 7 and day [14th] after similarly, and each parameter of triglyceride (TG) and the blood sugar level (BG) was measured. Furthermore, it dissected and collected blood and each cholesterol fraction was measured on the 15th.
[0034] (A result and consideration) The significant fall of TG was shown from the 4th after compound 1 medication, and the operation was maintained till the 14th. Each concentration change in the plasma after 14 day **** is shown in Table 5 and 6. The compound 1 showed the significant fall of TG as compared with control, and non-HDL also fell intentionally. On the other hand, although TC showed the downward tendency and HDL showed the upward tendency, a big change was not seen. It was shown that a compound 1 has a lipid-metabolism improvement operation also in the normal animal. In addition, change was not seen for the blood sugar level after **** during 14 days to control. Having only a lipid-metabolism improvement operation was suggested in the animal which has the normal blood sugar level from this, without a compound 1 showing a blood-sugar fall operation. .
[0035]
表５　　１４日連投後の各パラメーター濃度変化

被験薬剤	ＴＧ(mg/dl) (変化率:%)	ＢＧ(mg/dl) (変化率:%)
コントロール	208.62±23.48 (100)	101.65±2.77 (100)
化合物１ 300mg/kg	103.92±8.96 (50)*	106.62±2.21 (105)

Each eight groups *:p<0.01 vs Control [0036]
Table 6 Plasma cholesterol concentration change after 14 day ****
_____ A test drug TC (mg/dl) HDL (mg/dl) non-HDL (mg/dl) (Rate-of-change:%) (rate-of-change:%) (rate-of-change:%)
_____ Control 61.92**3.03 35.66**1.85 26.26**2.53 (100) (100) (100) Compound 1 300mg/kg 56.95**4.71 38.10**3.95 18.85**1.32 (92) (107) (72) **_____ Each eight groups **:p<0.05 vs Control [0037] The example of prescription of this invention physic is shown below.
(Example of prescription 1) Tablet (composition)
A compound 1 50mg lactose 72 corn starches 18 hydroxypropylcellulose 5 carboxymethyl-cellulose calcium 4 magnesium stearates 1_____sum 150mg [0038] Compound 1 200 g, lactose 288 g, corn starch 72 g was uniformly mixed using the fluidized bed granulator. To this 10 % hydroxypropylcellulose solution 200 g was sprayed and corned.

After xeransis and 20 It is carboxymethyl-cellulose calcium to through and this about the screen of a mesh. 16 g, magnesium stearate 4 g was added, and it mixed and considered as the end of a making tablet. Usuki of 7.5 mm x 9.0 R is used for this end of a making tablet by the rotary tableting machine, and it is per one lock. It considered as the tablet of 150 mg.
[0039]
[Effect of the Invention] The 1 and 4-screw [- [(3, 5-dioxo - 1, 2, and 4-****** diazo lysine-2-****)methyl] phenoxy]-2-butene or its salt permitted pharmaceutically of this invention has a good lipid-metabolism improvement operation, and is useful to the improvement of the abnormalities in a lipid metabolism, such as hyperlipidemia. [4] It is especially useful as a prevention / treatment agent of low HDL ****. Furthermore, a prevention and treatment of the hyperlipidemia which joins from diabetes are expected becoming a useful medicine. Therefore, this invention medicine is useful as prevention / treatment agents, such as kidney morbus including brain arteriosclerosis, such as ischemic heart disease, such as the morbus (for example, high triglyceride ****, hypercholesterolemia, low HDL ****, etc.) which presents the abnormalities of a lipid metabolism, for example, hyperlipidemia, an obesity and the morbus with which originate unusually [a lipid metabolism] and aggravation of a symptom is expected to be, for example, arteriosclerosis, a myocardial infarction, and the stenocardia, and a cerebral infarction, or an aneurysm, and a nephrotic syndrome,.

Field

[The technical field to which invention belongs] this invention relates to the lipid-metabolism improvement agent which makes an active principle a 1 and 4-screw [- [(3, 5-dioxo - 1, 2, and 4-****** diazo lysine-2-****)methyl] phenoxy]-2-butene or its salt permitted pharmaceutically. [4]

Technique

[Description of the Prior Art] The arteriosclerosis nature morbus is the morbus positioned in the high precedence of the cause of death, a upward tendency is presented with change of eating habits, and the research of its prevention and treatment is advanced. Hyperlipidemia is known as the first risk factor of the arteriosclerosis nature morbus or a lock out nature heart disease. According to the second report (ATP II) of the U.S. cholesterol educational program technical committee in 1993 As positive risk factor of the coronary-arteries morbus, ** quantity LDL cholesterol, ** Age (those who are the female who greeted the menopause at 45 or more years old of males, 55 or more years old of female, and the early stage, and have not received the estrogen replacement therapy), ** Family-history [of the coronary-arteries morbus], ** smoking, ** hypertension, ** low HDL cholesterol (below 35mg / dl), and ** diabetes ** is mentioned, and high HDL cholesterol (>=60mg/dl) is shown as negative risk factor. That is, the high LDL cholesterol and low HDL cholesterol (below 35mg / dl) which are the abnormalities of a lipid metabolism become the big factor of the coronary-arteries morbus, and it is reported on the contrary that high HDL cholesterol (>=60mg/dl) works to a prevention of the coronary-arteries morbus.
[0003] Therefore, it is expected that normalization of the lipid metabolism containing an improvement of the lipid metabolism in hyperlipidemia, i.e., a fall of LDL value and elevation of HDL value, reduces the risk of the arteriosclerosis nature morbus. Especially, in a diabetic, the arteriosclerosis nature morbus of a core and a brain serves as the direct cause of death in many cases, and the importance of the prevention and treatment of the hyperlipidemia which joins from diabetes is pointed out as diabetes is further mentioned as positive risk factor of the aforementioned coronary-arteries morbus (a diagnosis, treatment Vol.80(9), 1692-1696 (1992)).
[0004] Although the first phase of the treatment of the hyperlipidemia which joins from diabetes is the alimentary therapy, in many cases, the pharmacotherapy is needed further and various hyperlipidemia therapeutic drugs are used. However, in a commercial hyperlipidemia therapeutic drug, cautions are needed in many cases in respect of the safety of a side effect or the combined use with other agents (a diagnosis, treatment Vol.80(9), 1692-1696 (1992)). The pioglitazone (pioglitazone) or ********** (troglitazone) which is the thiazolidinedione compound with which the development is furthered as a blood-sugar fall

agent which has an insulin sensitivity potentiation having the triglyceride fall operation in blood is known (Arzneim.-forsch./Drug Res. – 40 (I) –) There is no report about the influence affect lipid metabolisms, such as LDL of Nr.2 (1990) and Diabetes, Vol.37, and 1549-58 thing (1988), and HDL. That is, the medicine it has the medicine and an improvement operation of sufficient abnormalities in a lipid metabolism in addition to a blood-sugar fall operation is not yet known.

[0005] on the other hand – international – public presentation – WO – 94 – /– 25448 – No. – an official report – **** – the above – thiazolidinedione – a compound – completely – structure – differing – one – four – - – a screw – [– four – - – [(3, 5-dioxo - 1, 2, and 4-****** diazo lysine-2-****) – a methyl –] – a phenoxy –] – - – two – - – a butene – containing – being new – a screw However, about the lipid-metabolism improvement operation of these compounds, neither indication nor suggestion is carried out at all.

Effect

[Effect of the Invention] The 1 and 4-screw [- [(3, 5-dioxo - 1, 2, and 4-****** diazo lysine-2-****)methyl] phenoxy]-2-butene or its salt permitted pharmaceutically of this invention has a good lipid-metabolism improvement operation, and is useful to the improvement of the abnormalities in a lipid metabolism, such as hyperlipidemia. [4] It is especially useful as a prevention / treatment agent of low HDL ****. Furthermore, a prevention and treatment of the hyperlipidemia which joins from diabetes are expected becoming a useful medicine. Therefore, this invention medicine is useful as prevention / treatment agents, such as kidney morbus including brain arteriosclerosis, such as ischemic heart disease, such as the morbus (for example, high triglyceride ****, hypercholesterolemia, low HDL ****, etc.) which presents the abnormalities of a lipid metabolism, for example, hyperlipidemia, an obesity and the morbus with which originate unusually [a lipid metabolism] and aggravation of a symptom is expected to be, for example, arteriosclerosis, a myocardial infarction, and the stenocardia, and a cerebral infarction, or an aneurysm, and a nephrotic syndrome,.

TECHNICAL PROBLEM

[Problem(s) to be Solved by the Invention] The invention of the medicine with few side effects which improves the abnormalities (for example, hyperlipidemia) in a lipid metabolism which are the risk factor of the arteriosclerosis nature morbus is desired. It is anxious for the invention of a medicine having a fall operation of a hyperglycemia value and an improvement operation of the abnormalities in a lipid metabolism especially useful to the hyperlipidemia which joins from diabetes.

MEANS

[Means for Solving the Problem] The place where this invention person etc. examined medicinal action about a series of screw ****** diazo lysine derivative given in the above-mentioned international public presentation WO official report of No. 94/25448, A 1 and 4-screw [- [(3, 5-dioxo - 1, 2, and 4-****** diazo lysine-2-****)methyl] phenoxy]-2-butene (compound I) or its salt permitted pharmaceutically found out having a also unexpectedly good lipid-metabolism improvement operation, and completed this invention. [4] Especially as a lipid-metabolism improvement operation of compound I, the improvement operation of HDL value is remarkable.

[0008] That is, this invention is a lipid-metabolism improvement agent which makes an active principle a 1 and 4-screw [- [(3, 5-dioxo - 1, 2, and 4-****** diazo lysine-2-****)methyl] phenoxy]-2-butene (compound I) or its salt permitted pharmaceutically. [4] Moreover, this invention relates to low HDL **** prevention / treatment agent which makes an active principle compound I or its salt permitted pharmaceutically. Furthermore, this invention relates to prevention / treatment agent of the hyperlipidemia which joins from diabetes which makes an active principle compound I or its salt permitted pharmaceutically from compound I having a powerful blood-sugar fall operation.

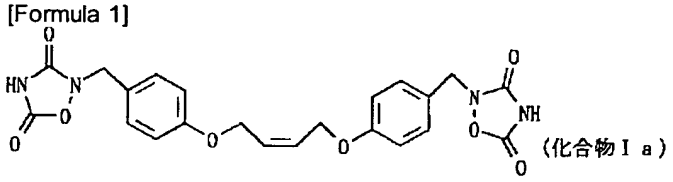
[0009]

[Embodiments of the Invention] It is as follows when this invention is explained further. (Active principle) The active principle of this invention physic is a 1 and 4-screw [- [(3, 5-dioxo - 1, 2, and 4-****** diazo lysine-2-****)methyl] phenoxy]-2-butene (compound I) or its salt permitted pharmaceutically, and is a well-known compound currently indicated by the international public presentation WO official report of No. 94/25448 with the manufacturing method. [4]

[0010] The **** (Z) field and the transformer (E) field based on presence of a double bond exist, and such things or mixture which were separated can be used for compound I as an active principle of this invention physic. It is the **** (Z) field (compound Ia) preferably shown by the following formula.

[0011]

[Formula 1]



(化合物Ｉａ)

[0012] As a salt of compound I permitted pharmaceutically, since it has an acid proton to a ****** diazo lysine ring, it is a salt with a base and, specifically, the salt with organic bases, such as the salt with inorganic bases, such as trivalent metals, such as alkaline earth metal, such as alkali metal, such as sodium and a potassium, magnesium, and calcium, and aluminum, a monomethylamine, an ethylamine, a dimethylamine, a diethylamine, a trimethylamine, a triethylamine, a monoethanolamine, a diethanolamine, a triethanolamine, a cyclohexylamine, a lysine, Compound I which is the active principle of this invention physic, or its salt permitted pharmaceutically may be isolated as a hydrate, various solvates, or matter of a crystal polymorphism, and all of these isolated things and mixture are included by this invention.

[0013] Actually, two or more crystal polymorphisms are checked by the **** (Z) field of compound I, and crystal B whose melting point besides crystal A whose melting point indicated by the example 10 of the above-mentioned international public presentation WO official report of No. 94/25448 is 139-144 degrees C is 166-7 degrees C, and crystal C which is 147-8 degrees C are also included by compound I of this invention. Especially, it is stable and crystal B which does not have hygroscopicity is desirable. Compound I of this invention can come to hand easily based on the technique which is well-known and was indicated by the aforementioned official report with the aforementioned official report. Moreover, the salt of compound I permitted pharmaceutically can be manufactured by the conventional method. When the hydrate, the solvate, or crystal polymorphism of compound I exists, these can be isolated to this contractor using the well-known separation / refining technique.

[0014] (Physic intended use) The lipid-metabolism improvement agent of this invention is a medicine which improves the abnormalities of the lipid metabolism produced for a certain ground. As a lipid metabolism being unusual, the increase in the abnormalities of the blood serum ******** roll value diagnosed as hyperlipidemia and/or blood serum triglyceride is mentioned, for example. The abnormalities with which independence, such as an increase in the very low density lipoprotein (VLDL-cholesterol) which accepts as blood serum cholesterol being unusual here as the increase in the total cholesterol and the balance of blood serum lipoprotein being unusual, and low extraordinary lipoprotein (LDL-cholesterol), a decrement of high density lipoprotein (HDL cholesterol) (especially HDL2-cholesterol), and an increase in remnant lipoprotein, or the plurality was combined are mentioned (clinical, research 72 volume 8 No., 1873 - 1879 pages). the operation whose medicine of this invention improves these abnormalities in a lipid metabolism -- it has a metabolism improvement operation of HDL cholesterol especially

[0015] Furthermore, in the diabetic, the abnormalities in a lipid metabolism join to the 1/3, presenting low HDL **** is known 10% (a diagnosis, treatment Vol.80(9), 1692-1696 (1992)), and since the medicine of this invention has a blood-sugar fall operation, it is useful for a prevention and treatment of the hyperlipidemia which joined from these diabetes. Therefore, it is prevention / treatment agent of the hyperlipidemia which joins from diabetes preferably as a lipid-metabolism improvement agent of this invention.

[0016] As concrete indication of this invention medicine, it is the morbus which presents the abnormalities of a lipid metabolism, for example, hyperlipidemia (for example, high triglyceride

****, hypercholesterolemia, low HDL ****, etc.), an obesity, etc. are mentioned. It is especially useful as a prevention / treatment agent of low HDL ****. Furthermore, as morbus with which originate unusually [a lipid metabolism] and aggravation of a symptom is expected to be, the kidney morbus including brain arteriosclerosis, such as ischemic heart disease, such as arteriosclerosis, a myocardial infarction, and the stenocardia, and a cerebral infarction, or an aneurysm, and a nephrotic syndrome etc. is mentioned, and it can be used also as a prevention / treatment agent of these morbus.

[0017] (A tablet-ized method, a medication method, dose) The physic of this invention blends compound I or its salt permitted pharmaceutically, and the support for medicine manufacture permitted pharmaceutically, and is prepared as physic constituents, such as taking orally, a parenteral solid-state, and a liquid.

[0018] As a solid-state constituent for the internal use by this invention, a tablet, the pilule, a capsule, a fine-grain agent, a granule, etc. are mentioned. In such a solid-state constituent, one or the active substance beyond it is mixed with at least one inactive diluent, for example, a lactose, a mannitol, grape sugar, hydroxypropylcellulose, a crystalline cellulose, various starch, a polyvinyl pyrrolidone, magnesium aluminometasilicate, etc. The constituent may contain the lysis or solubilizing agent like additives other than an inactive diluent, for example, a lubricant like a magnesium stearate, disintegrator like a calcium carboxymethyl cellulose, a stabilizing agent like a lactose, glutamic acid, or an aspartic acid according to a conventional method. Moreover, the film of glycocalyx, such as a cane sugar, gelatin, hydroxypropylcellulose, and a hydroxypropyl-methylcellulose free-wheel-plate rate, stomach solubility, or the enteric nature matter may cover the granulatio of a tablet, the pilule, a granule, and the capsule containing granulatio by the need. Moreover, in order to raise the solubility of a tablet, well-known solubilization processing can be performed and tablet-ization can also be performed.

[0019] The inactive diluent generally used as a component of a constituent in the opacifier permitted pharmaceutically, a solution agent, the suspension, the syrup, the elixir, etc. as a liquid constituent for internal use including the tablet gestalt, for example, a purified water, ethanol, etc. are included. This constituent may contain adjuvants, such as a wetting agent and a suspending agent, a sweetening agent, a flavor agent, an aromatic, and antiseptics in addition to an inactive diluent.

[0020] As injection for a parenteral administration, a water or non-water sterile solution agent, the suspension, and an opacifier are included. For example, distilled water for injection and a physiological saline are contained in a water solution agent and the water suspension. A propylene glycol, a polyethylene glycol, vegetable oil like olive oil, the alcohols like ethanol permitted pharmaceutically, and a surfactant like polyoxyethylene sorbitan fatty acid ester are contained in the solution agent of a non-aquosity, and the suspension. Such an aquosity and the constituent of a non-aquosity may contain adjuvants (for example, glutamic acid, an aspartic acid, etc.) and antiseptics, such as a wetting agent, a suspending agent, an emulsifier, a dispersant, a stabilizing agent (for example, lactose), lysis, or a solubilizing agent, in addition to these additives. These are sterility-ized by the combination or irradiation of filtration and a germicide which lets for example, a bacterium hold VCF pass. These can be again manufactured as a sterile solid-state constituent, and can also be made into the gestalt used by melting in sterile water or the sterile solvent for injection before use.

[0021] for using this invention for the purpose of [of the above-mentioned morbus] a prevention / treatment – usually – taking orally – or it is parenteral and a medicine is prescribed for the patient Although it changes with a patient's age, weight, a symptom, a curative effect, medication roots, etc. and it is suitably set up in consideration of these, usually, 0.1-100mg of dose is [in per adult day and internal use] preferably desirable 1-1000mg at 10-300mg and a parenteral administration, day, it is 1 time per or this is prescribed for the patient in 2 - several steps. Since the dose is changed according to the various conditions of the prevention purpose or others, an amount fewer than the above-mentioned dose domain may be enough as it.

[Translation done.]